

RECEIVED

OCT 16 2002

U.S. PATENT AND TRADEMARK OFFICE
LAW CENTER 1600/2900



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Harrington *et al.*

Appl. No: 09/484,331

Filed: January 18, 2000

For: **Compositions and Methods for Non-Targeted Activation of Endogenous Genes**

Art Unit: 1632

Examiner: Shukla, R.

Atty. Docket: 0221-0003L

SUPPLEMENTAL AMENDMENT UNDER 37 C.F.R. § 1.111

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Further to the Notice of Non-Responsive Reply dated October 3, 2002, Applicants submit the following Amendment and remarks, along with a copy of the corrected Sequence Listing and Computer Readable Copy, and a clean copy of the pending/under consideration claims.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 50-0622.

AMENDMENTS

Kindly enter the following amendments:

In the Specification:

On page 17, please replace the paragraph in lines 10-19 with the following paragraph:

FIG. 1. Schematic diagram of gene activation events described herein. The activation construct is transfected into cells and allowed to integrate into the host cell chromosomes at DNA breaks. If breakage occurs upstream of a gene of interest (e.g., Epo), and the appropriate activation construct integrates at the break such that its regulatory sequence becomes operably linked to the gene of interest, activation of the gene will occur. Transcription and splicing produce a chimeric RNA molecule containing exonic sequences from the activation construct and from the endogenous gene. Subsequent translation will result in the production of the protein of interest. Following isolation of the recombinant cell, gene expression can be further enhanced via gene amplification. The polyA tail is set forth in SEQ ID NO:33.

On page 21, please replace the paragraph in lines 6-17 with the following paragraph:

FIG. 13. Illustration depicting two transcripts produced from the integrated vectors described in Figures 12A-12G. DNA strands are depicted as horizontal lines. Vector DNA is shown as a black line. Endogenous genomic DNA is shown as a grey line. Rectangles depict exons. Vector-encoded exons are shown as open rectangles,

while endogenous exons are shown as shaded boxes. S/D denotes a splice donor site. Following integration, the vector encoded promoters activate transcription of the endogenous gene. Transcription resulting from the upstream promoter produces a spliced RNA molecule containing the vector encoded exon joined to the second and subsequent exons from an endogenous gene. Transcription from the downstream promoter, on the other hand, produces a transcript containing the sequences downstream of the integrated DNA joined to exon I and the subsequent exons from an endogenous gene. The polyA tails are set forth in SEQ ID NO:33.

On page 26, please replace the paragraph in lines 6-25 with the following paragraph:

FIG. 23A-23D. Example of a multi-Promoter/Activation Exon Vector. Each vector is illustrated schematically in its linearized form. Each horizontal line represents a DNA molecule. The arrows denote promoter sequences. Boxes indicate exons. Hatched boxes indicate untranslated regions. It is understood that the exons on these vectors may be untranslated, or may contain a start codon and additional codons as described herein. The following designations were used: splice donor site (S/D), vector promoter #1 (VP #1), vector promoter #2 (VP #2), vector promoter #3 (VP #3), and vector promoter #4 (VP #4). Individual vector activation exons are designated A, B, C, and D (SEQ ID NOS: 29-32, respectively). Each activation exon may contain a different structure. The structure of each activation exon and its flanking intron are shown below. It is understood, however, that any activation exon described herein, may be used on these vectors, in any combination and/or order, including exons that encode signal sequences,

partial signal sequences, epitope tags, proteins, portions of proteins, and protein motifs. Any of the exons may lack a start codon. In addition, while not illustrated in these examples, these vectors may contain a selectable marker and/or an amplifiable marker. The selectable marker may contain a poly (A) signal or a splice donor site. When present, the splice donor site may be located upstream or downstream of the selectable marker. Alternatively, the selectable marker may not be operably linked to a poly (A) signal and/or a splice donor site.

On page 30, please replace the sentence on line 9 with the following sentence:

FIG. 37A-37C. Nucleotide sequence of pRIG-T (SEQ ID NO:28).

REMARKS

Reconsideration of this Application is respectfully requested. The specification has been amended to incorporate sequence identification numbers and to correct a typographical error. The Sequence Listing and Computer Readable Copy have been submitted in accordance with 37 C.F.R. § 1.821. The amendments have been made to further prosecution in this application. No new matter has been added, thus, entry of the amendments is respectfully requested.

CONCLUSION

It is believed that a full and complete response has been made to the Notice and, as such, the present application is in condition for allowance. If the Examiner believes,